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Diet Quality and Survival in a Population-Based Bladder Cancer Study

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Abstract

Nutrition may impact bladder cancer survival. We examined the association between diet quality and overall and bladder cancer-specific survival. Bladder cancer cases from a population-based study reported pre-diagnosis diet. Diet quality was assessed using the 2010 Alternate Healthy Eating Index (AHEI-2010). Vital status was ascertained from the National Death Index. Adjusted hazard ratios (HR) and 95% confidence intervals (CI) were estimated using proportional hazards and competing risks regression models. Overall AHEI-2010 adherence was not associated with overall or bladder cancer-specific survival among non-muscle invasive bladder cancer (NMIBC) cases (HR, 1.00; 95% CI, 0.98–1.01; HR, 1.00; 95% CI, 0.97–1.02) or muscle invasive bladder cancer (MIBC) cases (HR, 0.99; 95% CI, 0.96–1.03; HR, 1.01, 95% CI 0.97–1.06). AHEI-2010 sugar-sweetened beverages adherence was associated with poorer overall survival (HR, 1.04; 95% CI, 1.01–1.08) and AHEI-2010 sodium adherence was associated with better overall and bladder cancer-specific survival after NMIBC diagnosis (HR, 0.92, 95% CI, 0.85–1.00; HR, 0.82; 95% CI, 0.68–0.98). AHEI-2010 fruit adherence was associated with poorer overall and bladder cancer-specific survival after MIBC diagnosis (HR, 1.17; 95% CI, 1.02–1.33; HR, 1.26; 95% CI, 1.03–1.55). Consumption of sugar-sweetened beverages, sodium, and fruit, not overall AHEI-2010 adherence, may be associated with bladder cancer survival.

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Keywords

bladder cancer; survival; mortality; Alternate Healthy Eating Index (AHEI); diet

Introduction

Despite recent advances in treatment, over 17,000 urinary bladder cancer deaths occur in the United States each year (1). Greater than 90% of bladder neoplasms arise from the urothelium of the bladder, with approximately 75% of diagnoses classified as non-muscle invasive bladder cancer (NMIBC) and 25% classified as muscle invasive bladder cancer (MIBC; ref. (2). Individuals with NMIBC generally have a favorable prognosis, with an average five-year overall survival of 70%, but a high risk of recurrence necessitating follow-up cystoscopy (1, 3). Individuals with MIBC have a worse prognosis, with an average five-year overall survival of approximately 50%, even with aggressive treatment (1). Given the high treatment costs and extensive post-treatment monitoring, bladder cancer is one of the most expensive cancers to treat on a per-patient basis in the United States (4). Understanding whether modifiable lifestyle behaviors, such as diet, are associated with bladder cancer survival may inform ways to improve disease prognosis.

A well-balanced diet has been shown to be inversely associated with all-cause and cancer-specific mortality among survivors of several common cancers, including breast, colorectal, and ovarian (5, 6). In the case of bladder cancer, pre- and post-diagnosis diet may affect tumor progression as excreted metabolites directly contact with the urothelium of the bladder (7). Bladder cancer cell culture and rodent models have demonstrated the antitumor effects of various components found in fruits, vegetables, and soy products (8–10). A cohort study reported consumption of raw broccoli before bladder cancer diagnosis was associated with better overall and disease-specific survival (11).

Several diet quality scoring systems have been developed to quantify healthy eating habits (5, 6). The 2010 Alternate Healthy Eating Index (AHEI-2010) is one such summary measure, designed to promote foods and macronutrients known to reduce chronic disease risk (12). Adherence to the AHEI-2010 has been found to be associated with improved survival after breast and colorectal cancer diagnosis (13, 14), but has not been previously evaluated for bladder cancer survival. We examined the association between pre-diagnosis adherence to the AHEI-2010 and overall and bladder cancer-specific survival using data from a population-based bladder cancer study.

Methods

Study Population

Bladder cancer cases, 25 to 79 years of age at diagnosis, enrolled in a population-based case-control study of bladder cancer conducted in New Hampshire, United States, were prospectively followed for survival outcomes. Study methods have been previously described (15–17). In brief, 1,228 residents newly diagnosed with bladder cancer were identified using the New Hampshire State Cancer Registry and enrolled in three phases, from July 1994 to June 1998 (Phase I), July 1998 to December 2001 (Phase II), and January 2002 to July 2004 (Phase III). Bladder cancer was classified according to the International Classification of Diseases (ICD), Ninth Revision (ICD-9: 188.0–188.9; ref. (18) or Tenth Revision (ICD-10: C670-C679; ref. (19) All participants completed an in-person structured interview shortly after bladder cancer diagnosis covering demographics, medical history, and lifestyle factors, including age at diagnosis, smoking status, and education (15). All participants provided written informed consent and the study was approved by the institutional review board at Dartmouth College.

Ascertainment of Bladder Cancer Diagnosis and Initial Treatment

A uniform pathology review was conducted by a single study pathologist (ARS) to confirm bladder cancer subtype urothelial carcinoma (previously known as transitional cell carcinoma) diagnosis, stage, and grade at time of diagnosis. Staging was based on the American Joint Commission on Cancer (AJCC) TMN guidelines (20). Grading was originally based on the 1973 World Health Organization (WHO) classification system, but was reclassified upon publication of the 1998 WHO/International Society of Urological Pathology (ISUP) grading system (21, 22). We excluded from our analyses participants determined to have non-urothelial carcinomas (n=23) or whose samples were not reviewed by the study pathologist (n=114). Bladder cancer treatment was acquired from the New Hampshire State Cancer Registry and classified by the study urologist.

Assessment of Dietary Intake

Usual pre-diagnosis diet was assessed as part of a personal interview conducted for the parent case-control study. Participants enrolled before 2000 were not administered a dietary assessment (n = 413). The diet instrument differed by study phase and participants completed the dietary assessment an average of 11.8 months after bladder cancer diagnosis. Participants in Phase II completed a Food Frequency Questionnaire (FFQ) developed by Harvard University (version 88GP; Harvard T.H. Chan School of Public Health, Boston, Massachusetts, United States; (23) and participants in Phase III completed a modified Diet History Questionnaire (DHQ) developed by the National Cancer Institute (NCI; National Institutes of Health, Bethesda, Maryland, United States; ref. 24). The FFQ ascertained average intake of 126 specified foods for the past 12 months, and calorie and nutrient composition were obtained by linkage to the United States Department of Agriculture (USDA) Nutrient Database for Standard Reference between 2004 to 2007 (23). The DHQ ascertained average consumption of 124 food items for the past five years, and calorie and nutrient composition were obtained by linkage to a sex- and portion-size-specific adapted version of the USDA 1994–1996 Continuing Survey of Food Intake by Individuals (24).

The AHEI-2010 Diet Quality Score

We assessed overall dietary quality using the AHEI-2010 scoring method (12, 25). The AHEI-2010 scores 11 dietary components from 0 to 10 based on published associations with reduced chronic disease risk. The AHEI-2010 awards points for greater daily consumption of vegetables (0 points for 0 servings/day and 10 points for ≥5 servings/day), fruits (excluding fruit juice; 0 points for 0 servings/day and 10 points for ≥4 servings/day), whole grains (0 points for 0 g/day and 10 points for 75 g/day in women and 90 g/day in men), nuts and legumes (0 points for 0 servings/day and 10 points for ≥1 servings/day), long-chain fats (0 points for 0 mg/day and 10 points for 250 mg/day), and polyunsaturated fats (PUFA; 0 points for ≤2 % of total energy intake and 10 points for ≥10 % of total energy intake). In contrast, the AHEI-2010 awards points for lower daily consumption of sugar-sweetened beverages and fruit juice (0 points or ≥1 servings/day and 10 points for 0 servings/day), red and processed meats (0 points for ≥1.5 servings/day and 10 points for 0 servings day), trans fat (0 points for ≥4 % of total energy intake and 10 points for ≤0.5 % of total energy intake), and sodium (0 points for highest decile and 10 points for lowest decile). For alcohol intake, heavy drinks (≥2.5 drinks/day for women and ≥3.5 drinks/day for men) receive a lower score and moderate drinkers (0.5–1.5 drinks/day in women and 0.5–2.0 drinks/day in men) receive a higher score to reflect the reported overall health benefits of moderate alcohol consumption (26). The AHEI-2010 total score ranges from 0 to 110, with low scores signifying nonadherence and high scores signifying adherence to the guidelines. The DHQ instrument assessed total fruit and total vegetable intake and we excluded fruit and vegetable items that did not adhere to the AHEI criteria (e.g., white potatoes and fruit desserts; ref. (12, 25)

Total Fluids

We calculated total fluid consumption by summing the serving sizes of all reported beverages. The FFQ and DHQ both assessed sugar-sweetened beverages, sugar-free soda, coffee, tea, milk, vegetable juice, diet fruit drinks, and alcohol. Participants who completed the FFQ were separately asked about daily water intake during the enrollment interview. The DHQ included non-carbonated and carbonated water consumption.

Study Outcomes

Vital status, date, and cause of death were obtained through linkage to the National Death Index (Centers for Disease Control and Prevention, Atlanta, Georgia, United States). Survival follow-up was complete through December 31, 2017. Cause of death was coded according to the ICD-10 (19). The primary outcome was death due to any cause, including bladder cancer (ICD-10: C67.0–67.9), non-bladder malignancy (ICD-10: C00-C66 and C68-C96), cardiovascular disease (ICD-10: I00-I99), respiratory system disease (ICD-10: J00-J99), and other (ICD codes not specified above or missing cause of death). The secondary outcome was disease-specific survival, for which the immediate or contributing cause of death was bladder cancer (ICD-10: C67.0-C67.9).

Statistical Analysis

Out of 678 pathology-confirmed urothelial carcinomas enrolled after 2000, a total of 637 (94.0%) participants completed the dietary assessment, including 295 cases who completed the FFQ and 342 cases who completed the DHQ. As recommended by the developers of the FFQ, participants were excluded from analyses if they had an extremely high (>3,500 kcal/day for women and >4,200 kcal/day for men) or low (<500 kcal/day for women and <800 kcal/day for men) daily caloric intake (n=37), if they left 70 or more diet questions blank (n=4), or if scanning errors occurred (n=3; ref. (27, 28) After these exclusions, a total of 593 participants were included in analysis (269 participants who completed the FFQ and 324 who completed the DHQ).

Due to the clinical, pathological, and molecular heterogeneity of bladder cancer, we analyzed NMIBC and MIBC separately. The majority of participants were diagnosed with NMIBC (AJCC stages 0a, 0is, and I) and these results are included in the main text. Results for MIBC (AJCC stages II, II, and IV) are reported in the supplemental material. Survival time was defined as months between bladder cancer diagnosis and the date of death or December 31, 2017. Cox proportional hazards regression was used to estimate hazard ratios (HR) per 1-unit increase in AHEI-2010 score and 95% confidence intervals (CI) of overall survival and Fine and Gray's competing risks regression was used to estimate HRs and 95% CI of bladder cancer-specific survival (29, 30). The proportional hazards assumption was confirmed for overall survival by evaluating linear trends in scaled Schoenfeld residuals (31), but was not evaluated for bladder cancer-specific survival (32).

We considered AHEI-2010 total score and the 11 individual AHEI-2010 dietary component scores as continuous variables. Separate regression models for NMIBC and MIBC were adjusted for factors known or hypothesized to be associated with diet quality and bladder cancer survival. For NMIBC, covariates included age at diagnosis (continuous), sex, smoking status (never, former, current), WHO/ISUP classification (carcinoma in situ [CIS], papillary urothelial of low malignant potential [PUNLMP], low-grade carcinoma, high-grade carcinoma, other), treatment (none/transurethral resection [TUR] only, systemic treatment), level of education (high school, college/graduate/professional), and daily energy intake (continuous). Systemic treatment included immunotherapy, intravesical chemotherapy, radiation, and/or cystectomy. For MIBC, model covariates were the same as for NMIBC, except AJCC stage (II/III, IV) was used instead of the WHO/ISUP grade and treatment was dichotomized as no cystectomy or cystectomy. The linearity of associations for the AHEI-2010 total score was verified by testing for the statistical significance of a quadratic term in the regression models.

We present HR estimates from separate regression models according to dietary instrument. Pooled HR estimates are also provided from a single regression model with inclusion of an indicator variable for dietary instrument (FFQ, DHQ) in addition to the covariates listed above for NMIBC and MIBC, respectively. We additionally considered effect modification by smoking status (never, ever), sex (men, women), and dietary instrument (FFQ, DHQ), separately, for NMIBC participants, but not for MIBC participants due to the small sample size.

Sensitivity analyses were performed for 359 NMIBC and 44 MIBC participants with reported BMI at study enrollment (kg/m^2) by additionally including BMI (continuous) as an adjustment variable in regression models. Separate sensitivity analyses were performed for dietary components expected to be strongly influenced by fluid intake by additionally including total fluid consumption as an adjustment variable in regression models. All tests were two-sided with p values <0.05 considered statistically significant. Analyses were conducted using R (version 3.6.2, R Foundation for Statistical Computing, Vienna, Austria).

The study was approved by the institutional review board at Dartmouth College and transferred to the institutional review board at Dartmouth-Hitchcock Medical Center. The study was performed in accordance with the Declaration of Helsinki. All participants provided written informed consent.

Results

Non-Muscle Invasive Bladder Cancer (NMIBC)

Population characteristics—In total, 527 NMIBC participants completed the dietary assessment, of whom 257 died, including 55 from bladder cancer. Most participants were older than 60 years of age at diagnosis, male, current or former smokers, diagnosed with AJCC stage 0a, and received TUR or no treatment (n for TUR = 420; n for untreated = 9; Table 1). Among NMIBC participants who completed the FFQ, a total of 122 deaths (50.4%) occurred over a median follow-up of 16.2 years after diagnosis. Among NMIBC participants who completed the DHQ, a total of 135 deaths (47.4%) occurred over a median follow-up of 13.9 years after diagnosis (Table 2). Mean AHEI-2010 total score and mean daily intake of the 11 AHEI-2010 dietary components were similar among those with NMIBC who completed the FFQ and DHQ (Table 3).

Association of the AHEI-2010 score with overall survival—Greater adherence to the AHEI-2010 was not associated with overall survival after NMIBC diagnosis (HR, 1.00; 95% CI, 0.98–1.01; Table 4, Supplemental Table S1). Smoking status, sex, and dietary instrument did not modify this association (Supplemental Tables S2, S3, and S4). Adherence to the AHEI-2010 sugar-sweetened beverages score was associated with poorer overall survival (HR, 1.04; 95% CI, 1.01–1.08) and adherence to the AHEI-2010 sodium score was associated with better overall survival (HR, 0.92; 95% CI, 0.85–1.00). HRs for the AHEI-2010 sugar-sweetened beverages and sodium component scores were not meaningfully different when additionally adjusted for total fluid consumption or for BMI (data not shown). We did find evidence that the association between the AHEI-2010 sugar-sweetened beverage guideline and overall survival differed according to sex ($p_{interaction}$, 0.03), with men showing a stronger association than women (HR for men, 1.07; 95% CI, 1.03–1.11; HR for women, 0.97, 95% CI, 0.90–1.05; Supplemental Table S3). There was also evidence that the association between the AHEI-2010 vegetable component score and overall survival differed according to the dietary instrument (HR for FFQ, 0.90; 95% CI, 0.83–0.98; HR for DHQ, 1.08; 95% CI, 0.98–1.19; $p_{interaction}$, 0.005; Supplemental Table S4). To examine the AHEI-2010 vegetable component score more carefully, we included only vegetables that were food items on both questionnaires, and evidence of effect modification persisted ($p_{interaction}$, 0.004; Supplemental Table S5).

Association of the AHEI-2010 score with bladder cancer-specific survival—For NMIBC participants, adherence to the AHEI-2010 was not associated with bladder cancer-specific death (HR, 1.00; 95% CI, 0.97–1.02; Table 4, Supplemental Table S6), with no evidence of effect modification by smoking status, sex, or dietary instrument (Supplemental Tables S2, S3 and S4). Adherence to the AHEI-2010 sodium component score was associated with better bladder cancer-specific survival after NMIBC diagnosis (HR, 0.82; 95% CI, 0.68–0.98). Additionally, adjusting the AHEI-2010 sodium component score for total fluid consumption did not change the results (data not shown). No statistically significant associations for NMIBC bladder cancer-specific survival were identified for the other dietary component scores (Table 4). Results were not meaningfully different when additionally adjusted for BMI (data not shown). Again, there was evidence that the association between the AHEI-2010 vegetable component score and bladder cancer-specific survival differed according to the dietary instrument (HR for FFQ, 0.67; 95% CI, 0.44–1.01; HR for DHQ, 0.92; 95% CI, 0.75–1.11; $p_{interaction}$, 0.01; Supplemental Table S4), which remained when including only vegetables that were food items on both questionnaires ($p_{interaction}$, 0.03; Supplemental Table S5).

Muscle Invasive Bladder Cancer (MIBC)

Population characteristics—A total of 66 MIBC participants completed the dietary assessment, of whom 52 died, including 26 from bladder cancer. Most were diagnosed with AJCC stage II and stage III carcinoma and underwent cystectomy (Supplemental Table S7). Among MIBC participants who completed the FFQ, a total of 23 deaths (85.2%) occurred over a median follow-up of 4.8 years after bladder cancer diagnosis. Among MIBC participants who completed the DHQ, a total of 29 deaths (74.4%) occurred over a median follow-up of 6.8 years after diagnosis (Supplemental Table S8). For MIBC, both FFQ and DHQ responders had a similar AHEI-2010 total score (Supplemental Table S9).

Association of the AHEI-2010 score with overall survival—Greater adherence to the AHEI-2010 was not associated with overall survival after MIBC diagnosis (HR, 0.99; 95% CI, 0.96–1.03; Supplemental Table S10). When considering the dietary component scores individually, adherence to the AHEI-2010 fruit score was associated with poorer overall survival (HR, 1.17; 95% CI, 1.02–1.33).

Association of the AHEI-2010 score with bladder cancer-specific survival— Adherence to the AHEI-2010 was not associated with bladder cancer-specific death after MIBC diagnosis (HR, 1.01; 95% CI, 0.97–1.06; Supplemental Table S11). Adherence to the AHEI-2010 fruit score was associated with poorer bladder cancer-specific survival after MIBC diagnosis (HR, 1.26; 95% CI, 1.03–1.55).

Discussion

In this cohort study of population-based NMIBC and MIBC cases, overall adherence to the AHEI-2010 was unrelated to overall or bladder cancer-specific survival. There was, however, evidence that certain dietary component scores were associated with survival. Greater adherence to the AHEI-2010 sodium guideline was associated with modestly improved overall and bladder cancer-specific survival among those with NMIBC. In contrast, greater adherence to the AHEI-2010 sugar-sweetened beverages guideline was associated with modestly poorer overall survival among those with NMIBC. Among those with MIBC, greater adherence to the AHEI-2010 fruit guideline was associated with poorer overall and bladder cancer-specific survival.

Current understanding of the relationship between diet quality and urothelial carcinoma survival is limited. Most investigations of bladder cancer survival have primarily focused on individual nutrients, supplements, or food groups with limited concordance (11, 33, 34).

Recently, a prospective cohort study conducted in the United States applied factor analysis to investigate the association between pre-diagnosis dietary behaviors and bladder cancer recurrence and progression among 595 individuals with NMIBC (35). Their findings suggest higher adherence to a Western dietary pattern was associated with higher risk of recurrence.

Diet quality has been examined in association with survival for other cancers. For example, a meta-analysis of non-urothelial neoplasms, including breast and colorectal, found higher pre- or post-diagnostic AHEI-2010 scores were associated with a 17% lower risk of cancer death (HR, 0.83; 95% CI, 0.81–0.86; ref. (36) Aside from tumor specific differences, the discrepancy of these findings with ours could be due to differences between study populations, including severity of disease, effects of cancer-specific treatment, physical activity, and comorbidities (1, 37–39).

In our study, lower sodium intake was associated with better overall and bladder cancer-specific survival after NMIBC diagnosis. Sodium is an essential nutrient that aids in normal physiological function and cellular homeostasis (40). Since the 1980s, the USDA and the United States Department of Health and Human Services have encouraged reduced sodium consumption to prevent hypertension and cardiovascular disease (41). The association between dietary sodium intake and survival after urothelial carcinoma, however, has not been well studied. While animal models have reported that sodium may promote bladder cancer proliferation, the mechanism between high sodium intake and bladder cancer remains poorly defined (42). In contrast to our findings, a retrospective hospital-based cohort study in Japan of 179 MIBC patients reported that preoperative serum sodium concentration ≤139 mEq/L was associated with poorer survival following radical cystectomy (43). The difference between their findings and ours could be due to differences in the distribution of stage and treatment or the fact that circulating serum sodium concentration is tightly regulated and an imprecise measurement of dietary sodium consumption (44). Furthermore, food frequency questionnaires may not accurately estimate dietary sodium (45).

Measured sugar-sweetened beverages in our study included non-diet soda, fruit juice, and other fruit drinks, such as fruit punch and lemonade. The DHQ, but not the FFQ, also asked about sweeteners in coffee and tea, such as sugar and honey. As a discretionary food, sugar-sweetened beverages provide little nutrient value and excess intake has been linked to numerous adverse outcomes including weight gain, type 2 diabetes, and cardiovascular disease (46–48). Studies of cancer patients, including those with colorectal and upper aerodigestive tract cancers, have reported that lower pre- or post-diagnosis consumption of sugar-sweetened beverages is associated with lower risk of all-cause death (49, 50). In contrast, we found adherence to the AHEI-2010 sugar-sweetened beverages guideline (i.e., lower intake) was associated with poorer overall survival. This association was slightly modified by sex, although the biological basis behind this remains uncertain. The primary source of sugar-sweetened beverages in this population was fruit juice. In this study, as well as in the case of bladder cancer in particular, it is unclear whether exposure to beneficial urinary antioxidants, flavonoids, or phytochemicals from fruit juice potentially negate some detrimental effects of added sugar (51, 52). For example, apple polyphenols have been shown to induce cell cycle arrest and apoptosis in bladder cancer animal models (53). Similar to our study's finding on survival, the Adventist Health Study in California reported that higher consumption of sweetened real fruit juices was associated with lower risk of developing bladder cancer (54).

Our analysis of 66 MIBC cases suggested that greater adherence to the AHEI-2010 fruit guideline or higher intake was associated with 17% higher risk of death due to any cause and 26% higher risk of death due to bladder cancer. A cohort study conducted at Roswell Park Cancer Center in the United States observed no association between total fruit intake and overall or disease-specific survival in 239 local and advanced bladder cancer patients (11), which is consistent with our findings for NMIBC, but not MIBC. The Roswell Park study also reported no association between vegetable intake and survival outcomes, similar to our analysis. In addition to survival, fruits and vegetables have been extensively studied in association with bladder cancer risk. A meta-analysis of 17 bladder cancer cohort studies reported no association between bladder cancer risk and total vegetable or fruit consumption (55), while a separate pooled analysis of 13 cohort studies found evidence that higher total fruit intake may reduce the risk of bladder cancer among women (56). Additional studies are needed to establish the mechanistic effects of fruit on bladder cancer.

Our study has several strengths. First, we ascertained survival time for bladder cancer cases from a population-based case-control study, which enhances the generalizability of our findings to populations comparable to New Hampshire, United States. Second, participants were diagnosed between 1998 and 2004, allowing for long-term follow-up to investigate survival with complete vital status ascertainment from administrative records. Moreover, this study examined overall dietary quality instead of single nutrients and food components, which more accurately reflects that individuals eat foods in combination and not in isolation. Dietary patterns also capture the cumulative and interactive effects of nutrients while acknowledging the possibility of food substitution (57).

A limitation of our study is that different dietary questionnaires were used during different data collection phases. We saw some evidence of effect modification by dietary instrument between the AHEI-2010 vegetable component score and overall and bladder-cancer specific survival that may be the consequence of different questionnaire formats and nutrient composition measures. Both instruments, however, have been externally validated (23, 58). The dietary questionnaires were administered once at the time of recruitment in the parent case-control study, and participants were instructed to report on usual pre-diagnosis diet. We did not ascertain diet again after diagnosis. Exposure misclassification is possible, particularly over time, as dietary habits may change substantially after diagnosis and treatment. Similarly, smoking status was only collected once, and smoking behaviors may have changed during the period after diagnosis. Another limitation is that BMI at study enrollment was incompletely ascertained (31.9% of NMIBC and 33.3% of MIBC cases were missing BMI) and not incorporated in our final analysis. Low BMI (<18.5 kg/m^2) before cystectomy in MIBC cases (59) and higher BMI in NMIBC cases (60) have been reported to be associated with poorer overall and bladder cancer-specific survival. Our sensitivity analyses that adjusted for BMI among participants with available BMI showed no meaningful differences (61). Additionally, physical activity, previously reported to be associated with better bladder cancer-specific survival (62), was not available.

We investigated overall and bladder cancer-specific survival but did not assess bladder cancer recurrence. More than 70% of NMIBC patients experience a bladder cancer recurrence within two years of diagnosis, making recurrence a crucial endpoint to examine in future studies of dietary exposures (3). The small sample size of MIBC cases in this analysis resulted in limited statistical power. Accordingly, our observation of an association between the AHEI-2010 fruit component and MIBC survival outcomes should be interpreted with caution, particularly in the presence of multiple statistical comparisons.

In conclusion, pre-diagnosis diet quality as measured by the AHEI-2010 was unrelated to overall and bladder cancer-specific survival in this population-based cohort. Adherence to AHEI-2010 sugar-sweetened beverages and AHEI-2010 sodium guidelines may impact survival following NMIBC diagnosis while adherence to AHEI-2010 fruit guidelines may affect survival following MIBC diagnosis. Further research is needed to elucidate the biological effects, if any, of pre- and post-diagnosis diet on the tumor and its microenvironment, alone and in combination with bladder cancer treatment. Although studies of the consistent association between diet quality and mortality from cancer or other chronic diseases reinforce the importance of healthy nutrition in primary and secondary prevention, our findings suggest some distinct associations that may reflect the unique experience of bladder cancer survivors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data availability statement:

The data that support the findings of this study are available from the corresponding author, M.N.P., upon reasonable request.

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Table 1.

Demographic and clinical baseline characteristics of diagnosed NMIBC cases (n = 527) in a New Hampshire population-based study according to dietary instrument.[a]

	All (n = 527)		Dietary Instrument[b] Harvard FFQ (n = 242)		NCI DHQ (n = 285)	
Characteristic	***n***	**(%)**	***n***	**(%)**	***n***	**(%)**
Age at Diagnosis, years [c]						
Mean (SD)	63.8	(9.8)	61.7	(9.6)	65.6	(9.6)
<50	46	(8.7)	26	(10.7)	20	(7.0)
50–59	121	(23.0)	64	(26.4)	57	(20.0)
60–69	182	(34.5)	97	(40.1)	85	(29.8)
70–79	178	(33.8)	55	(22.7)	123	(43.2)
Sex						
Male	388	(73.6)	177	(73.1)	211	(74.0)
Female	139	(26.4)	65	(26.9)	74	(26.0)
Education						
High School	253	(48.0)	126	(52.1)	127	(44.6)
College / Graduate / Professional	271	(51.4)	113	(46.7)	158	(55.4)
Unknown[d]	3	(0.6)	3	(1.2)	0	(0.0)
Smoking Status						
Never	82	(15.6)	39	(16.1)	43	(15.1)
Former	282	(53.5)	124	(51.2)	158	(55.4)
Current	158	(30.0)	79	(32.6)	79	(27.7)
Unknown[d]	5	(0.9)	0	(0.0)	5	(1.8)
Body Mass Index, kg/m ^{2}						
< 18.5	2	(3.8)	2	(0.8)	0	(0.0)
18.5–24.9	94	(17.8)	17	(7.0)	77	(27.0)
25.0–29.9	160	(30.4)	41	(16.9)	119	(41.8)
> 30.0	103	(19.5)	18	(7.4)	85	(29.8)
Unknown	168	(31.9)	164	(67.8)	4	(1.4)
AJCC Stage						
0is	32	(6.1)	15	(6.2)	17	(6.0)
0a	408	(77.4)	180	(74.4)	228	(80.0)
I	87	(16.5)	47	(19.4)	40	(14.0)
Tumor Grade [e]						
CIS	33	(6.3)	15	(6.2)	18	(6.3)
PUNLMP	155	(29.4)	71	(29.3)	84	(29.5)
Low Grade Carcinoma	187	(35.5)	93	(38.4)	94	(33.0)
High Grade Carcinoma	152	(28.8)	63	(26.0)	89	(31.2)
Treatment						

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	All (n = 527)		Dietary Instrument[b] Harvard FFQ (n = 242)		NCI DHQ (n = 285)	
Characteristic	***n***	**(%)**	***n***	**(%)**	***n***	**(%)**
None / TUR Only[f]	429	(81.4)	200	(82.6)	229	(80.4)
Systemic / Cystectomy[g]	98	(18.6)	42	(17.4)	56	(19.6)

Abbreviations: AJCC, American Joint Committee on Cancer; CIS, carcinoma in-situ; DHQ, Diet History Questionnaire; FFQ, Food Frequency Questionnaire; NCI, National Cancer Institute; NMIBC, non-muscle invasive bladder cancer; PUNLMP, papillary urothelial neoplasm of low malignant potential; TUR, transurethral resection.

[a]Percentages may not sum to 100% because of rounding.

[b]The type of diet questionnaire differed by study phase. Harvard FFQ was administered July 1998 to December 2001 and NCI DHQ was administered January 2002 to July 2004.

[c]Age range for Harvard FFQ was 32 to 74. Age range for NCI DHQ was 39 to 79.

[d]Participants with unknown education and smoking status were excluded from survival analyses.

[e]Determined using the World Health Organization/International Society of Urological Pathology classification.

[f]Number of no treatment were as follows: Harvard FFQ, 7; NCI DHQ, 2. Number of TUR only treatment were as follows: Harvard FFQ, 193; NCI DHQ, 227.

[g]Systemic treatment includes immunotherapy, intravesical chemotherapy, and/or radiation therapy.

Table 2.

Median follow-up time and cause of death of diagnosed NMIBC cases in a New Hampshire population-based study according to dietary instrument.

	All (n = 527)		Dietary Instrument[a] Harvard FFQ (n = 242)		NCI DHQ (n = 285)	
Median Follow-Up Time, years[b]	14.1		16.2		13.9	
Deaths, n	257		122		135	
Cause of Death, n (%)[c,d]						
Bladder Cancer	55	(21.4)	27	(22.1)	28	(20.7)
Non-Bladder Malignancy	75	(29.2)	42	(34.4)	33	(24.4)
Cardiovascular Disease	49	(19.1)	18	(14.8)	31	(23.0)
Respiratory System Disease	24	(9.3)	12	(9.8)	12	(8.9)
Other	54	(21.0)	23	(18.9)	31	(23.0)

Abbreviations: DHQ, Diet History Questionnaire; FFQ, Food Frequency Questionnaire; ICD-10, International Classification of Diseases, 10th revision; NCI, National Cancer Institute; NMIBC, non-muscle invasive bladder cancer.

[a]The type of diet questionnaire differed by study phase. Harvard FFQ was administered July 1998 to December 2001 and NCI DHQ was administered January 2002 to July 2004.

[b]Follow-up time is defined as years between bladder cancer diagnosis and date of death or December 31, 2017, whichever comes first.

[c]Percentages are among those with an observed death. May not sum to 100% because of rounding.

[d]ICD-10 codes that define cause of death are as follows: bladder cancer C67.9, non-bladder malignancy C00-C66 and C68-C96, cardiovascular disease I00-I99, respiratory system disease J00-J99. Other includes ICD codes not specified above and includes 3 participants missing cause of death.

Table 3.

AHEI-2010 total and dietary component scores for NMIBC cases in a New Hampshire population-based study according to dietary instrument.

			Dietary Instrument[b]			
	All (n = 527)		Harvard FFQ[c] (n = 242)		NCI DHQ[d] (n = 285)	
Dietary Component[a]	**Mean**	**(SD)**	**Mean**	**(SD)**	**Mean**	**(SD)**
AHEI-2010 Total Score	47.1	(10.5)	46.4	(10.6)	47.7	(10.5)
Vegetables[e]	3.7	(2.4)	4.5	(2.6)	3.1	(2.0)
Fruits[e]	3.4	(2.6)	3.1	(2.4)	3.7	(2.7)
Whole Grains	2.0	(2.0)	2.0	(2.5)	2.0	(1.5)
Sugar-Sweetened Beverages[f]	3.0	(3.6)	2.9	(3.7)	3.1	(3.6)
Nuts, Legumes, and Soy	6.7	(3.3)	5.3	(3.3)	7.9	(2.8)
Red/Processed Meat	3.9	(2.8)	4.0	(2.8)	3.9	(2.9)
Trans Fat	3.8	(2.1)	2.7	(1.5)	4.7	(1.9)
Long-Chain (n-3) Fats	4.9	(3.5)	6.9	(3.4)	3.2	(2.7)
PUFA	6.4	(1.8)	5.9	(1.4)	6.9	(1.9)
Sodium	4.5	(2.9)	4.5	(2.9)	4.5	(2.8)
Alcohol	4.7	(3.6)	4.6	(3.4)	4.8	(3.7)

Abbreviations: AHEI-2010, Alternate Healthy Eating Index, 2010 version; DHQ, Diet History Questionnaire; FFQ, Food Frequency Questionnaire; NCI, National Cancer Institute; NMIBC, non-muscle invasive bladder cancer; PUFA, polyunsaturated fats.

[a] According to Chiuve SE et al., 2012 (ref. 12).

[b] The type of diet questionnaire differed by study phase. Harvard FFQ was administered July 1998 to December 2001 and NCI DHQ was administered January 2002 to July 2004.

[c] Ranges for the Harvard FFQ were as follows: AHEI-2010 Total Score, 21.1–76.2; Vegetables, 0.3–10.0; Fruits, 0.0–10.0; Whole Grains, 0.0–10.0; Sugar-Sweetened Beverages, 0.0–10.0; Nuts, Legumes, and Soy, 0.0–10.0; Red/Processed Meat, 0.0–10.0; *Trans* Fat, 0.0–6.4; Long-Chain (n-3) Fats, 0.0–10.0; PUFA, 0.0–10.0; Sodium, 0.0–10.0; Alcohol, 0.0–10.0.

[d] Ranges for the NCI DHQ were as follows: AHEI-2010 Total Score, 15.6–74.4; Vegetables, 0.2–10.0; Fruits, 0.0–10.0; Whole Grains, 0.0–10.0; Sugar-Sweetened Beverages, 0.0–10.0; Nuts, Legumes, and Soy, 0.0–10.0; Red/Processed Meat, 0.0–9.60; *Trans* Fat, 0.0–8.7; Long-Chain (n-3) Fats, 0.0–10.0; PUFA, 2.7–10.0; Sodium, 0.0–10.0; Alcohol, 0.0–10.0.

[e] Does not include juice.

[f] Includes fruit juice.

Table 4.

Association between AHEI-2010 dietary component scores[a] and overall or bladder cancer-specific survival among NMIBC cases in a New Hampshire population-based study.[b]

	Overall Survival[c]			Bladder Cancer-Specific Survival[d]		
Dietary Component	**Hazard Ratio[e,f]**	**(95% CI)**	***p*-value**	**Hazard Ratio[e,f]**	**(95% CI)**	***p*-value**
AHEI-2010 Total Score	1.00	(0.98–1.01)	0.54	1.00	(0.97–1.02)	0.73
Vegetables[g]	0.96	(0.90–1.03)	0.28	1.04	(0.90–1.20)	0.57
Fruits[g]	1.00	(0.95–1.06)	0.91	1.01	(0.90–1.15)	0.83
Whole Grains	0.99	(0.93–1.07)	0.88	1.00	(0.87–1.14)	1.00
Sugar-Sweetened Beverages[h]	1.04	(1.01–1.08)	0.02	1.02	(0.95–1.10)	0.56
Nuts, Legumes, and Soy	0.99	(0.95–1.03)	0.62	0.96	(0.88–1.05)	0.36
Red/Processed Meat	0.98	(0.93–1.03)	0.39	1.00	(0.89–1.11)	0.93
Trans Fat	0.98	(0.91–1.05)	0.52	1.12	(0.94–1.33)	0.21
Long-Chain (n-3) Fats	1.01	(0.97–1.06)	0.55	0.95	(0.86–1.04)	0.28
PUFA	1.01	(0.94–1.09)	0.77	0.96	(0.82–1.12)	0.57
Sodium	0.92	(0.85–1.00)	0.04	0.82	(0.68–0.98)	0.03
Alcohol	0.97	(0.93–1.00)	0.07	1.02	(0.94–1.09)	0.68

Abbreviations: AHEI-2010, Alternate Healthy Eating Index, 2010 version; CIS, carcinoma in-situ; DHQ, Diet History Questionnaire; FFQ, Food Frequency Questionnaire; ISUP, International Society of Urologic Pathology; NCI, National Cancer Institute; NMIBC, non-muscle invasive bladder cancer; PUFA, polyunsaturated fats; PUNLMP, papillary urothelial neoplasm of low malignant potential; TUR, transurethral resection; WHO, World Health Organization.

[a] According to Chiuve SE et al., 2012 (ref. 12).

[b] Pooled analysis includes both participants who completed the Harvard FFQ and participants who completed the NCI DHQ.

[c] Number of deaths from any cause for Harvard FFQ respondents is 120 of 239 at risk. Number of deaths from any cause for NCI DHQ respondents is 133 of 280 at risk.

[d] Number of bladder cancer deaths for Harvard FFQ respondents is 26 of 239 at risk and number of competing deaths is 94 of 239 at risk. Number of bladder cancer deaths for NCI DHQ respondents is 28 of 280 at risk and number of competing deaths is 105 of 280 at risk.

[e] Hazard ratio per 1 unit increase in AHEI-2010 dietary component score.

[f] Adjusted for sex, age at diagnosis, smoking status (never, former, current), WHO/ISUP classification (CIS, PUNLMP, low grade carcinoma, high grade carcinoma), treatment (none/TUR only, systemic), education (high school, college/graduate/professional), energy (kcal/day), and dietary instrument.

[g]Does not include juice.

[h]Includes fruit juice.